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# Biomarkers for early detection of cardiac surgery-associated acute kidney injury

Reza Tavakoli<sup>1,2</sup>, Guillaume Lebreton<sup>1</sup>

<sup>1</sup>Department of Cardiovascular and Thoracic Surgery, Pitié Salpêtrière University Hospital, Assistance Publique, Hôpitaux de Paris (APHP), Institut de Cardiologie, Paris, France; <sup>2</sup>Institute of Veterinary Physiology and Zurich Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

*Correspondence to:* Reza Tavakoli, MD, PhD. Department of Cardiovascular and Thoracic Surgery, Pitié Salpêtrière University Hospital, Assistance Publique, Hôpitaux de Paris (APHP), Institut de Cardiologie, 56 Boulevard Vincent Auriol, 75013 Paris, France. Email: reza.tavakoli@uzh.ch.

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Acute kidney injury (AKI) is an increasingly encountered clinical situation in the intensive care setting. In this context in addition to sepsis, cardiac surgery-associated AKI (CSA-AKI) is one of the most common causes of acute renal failure (1). Depending on the definition of AKI and preexisting risk factors, the incidence CSA-AKI varies between 3% and 40% of patients undergoing open heart as well as transcatheter aortic valve implantation (1,2). Several diagnostic systems have defined AKI according to similar criteria of kidney function (3,4). The last consensus criteria have been proposed by Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (5). KDIGO criteria for diagnosis and staging reuse the Acute Kidney Injury Network (AKIN) system (4) with minor modifications. According to KDIGO, a broad definition of AKI includes one of the following observations: (I) an increase in serum creatinine (SCr) by  $\geq 0.3$  mg/dL ( $\geq 26.5$   $\mu\text{mol/L}$ ) within 48 h, or (II) an increase in SCr to  $\geq 1.5$  times baseline within the previous 7 days, or (III) urine volume  $\geq 0.5$  mL/kg/h for 6 h (6). Although a relatively high proportion of patients undergoing open heart surgery develop postoperative minor forms of CSA-AKI, only 1% of these patients present a severe AKI necessitating renal replacement therapy (RRT) (7). Severe CSA-AKI is associated with increased perioperative mortality, prolonged length of stay in the intensive care unit (ICU) and in hospital, and increased cost of care (8). The risk of death and hospital readmissions associated with AKI remains high even 5 to 10 years after cardiac surgery regardless of other

risk factors, even for those patients with complete renal recovery (7).

The pathogenesis of CSA-AKI is complex and multifactorial. Several pre-, intra- and post-operative factors may negatively affect the development of CSA-AKI. Predisposing factors such as age, chronic kidney disease, diabetes, arterial hypertension and atherosclerosis, intra-operative characteristics including the type of cardiac surgery, surgical time and cardiopulmonary bypass (CPB) technique and management (9), as well as postoperative mishaps like hemodynamic instability, use of nephrotoxic drugs or anemia may also contribute to CSA-AKI (8). Besides, CBP per se by activating the release of inflammatory mediators and by inducing hemodilution can favor the occurrence of AKI, especially in patients presenting with predisposing factors (9). The prompt diagnosis of AKI at its initial stage after cardiac surgery is not easy to establish. However, early detection of CSA-AKI can help limiting renal injury by establishing appropriate corrective therapies of reversible factors that contribute to AKI and thus improving patient prognosis. For early detection of CSA-AKI, based on their previous reports (4), the Cleveland group introduced new and expanded predictive models using pre- and intra-operative variables (10). In their study, 18 pre-operative and 4 intra-operative characteristics were included in four models of either pre-operative data alone or combined pre- and intra-operative data to predict either single primary endpoint of dialysis therapy or composite primary endpoint of dialysis

therapy or doubling of SCr (10). Interestingly, in the studied population the 2 models predictive of the dialysis therapy endpoint using presurgical only or pre- and intra-surgical combined variables showed excellent discrimination and good calibration, whereas the 2 models predictive of the composite endpoint (doubling of SCr level or dialysis therapy) showed good discrimination, but suboptimal calibration (10). These predictive models developed in a US population could not be externally validated in a European population (11). The two predictive models for single primary endpoint of dialysis therapy (pre-operative data alone or combined pre- and intra-operative data) demonstrated only a good discriminative capacity (11). In contrast to the report of Demirjian (10), the two models (pre-operative data alone or combined pre- and intra-operative data) predicting the composite endpoint of either dialysis therapy or a doubling of SCr level showed fair discriminative capacity (11). Moreover, a lack of calibration was observed not only in the two predictive models for single primary endpoint of dialysis therapy but also in those predicting the composite endpoint of either dialysis therapy or a doubling of SCr level (11). These discrepancies between the studies are mainly due to the inevitable differences in patients' characteristics and changes in medical technology and standards of care over time. Therefore, recalibration by readjustment to local patients' characteristics and structural model revisions by adding new variables might be necessary to enhance the applicability of the predictive models.

Along these lines, several investigators have focused on the identification of biomarkers beyond SCr for early detection of AKI. This interest is motivated by the fact that a significant rise in SCr marks an already advanced stage of kidney injury. Moreover, in elderly and malnourished patients the rise in SCr might be minimal and considerably delayed. Another reason for searching other biomarkers of AKI is the distinction made between "renal failure" and "renal injury". In fact, renal injury may have various clinical consequences without significant deterioration of renal function (12). Ideal biomarkers may be expected to fulfill simple criteria: (I) rapid, inexpensive, and noninvasive or minimally invasive measurement technique; (II) sensitive to establish an early and specific diagnosis but remaining elevated for a long time to allow diagnosis; (III) specific cutoff values, with an increase that is proportional to the degree of damage and a high gradient to allow risk stratification; (IV) associated with a known biological mechanism (plausibility); (V) capability to predict clinical outcomes and therapy response (12). These considerations

imply that a combination of biomarkers rather than a single pathognomonic one may be necessary for early detection of AKI. Numerous biomarkers have been reported to allow the diagnosis of AKI at its early stages. These biomarkers are of biochemical or biomechanical nature.

Biochemical markers include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC), kidney injury molecule-1 (KIM-1), monocyte chemotactic peptide-1 (MCP-1), N-acetyl- $\beta$ -D-glucosaminidase (NAG), interleukin-18 (IL-18), liver-type fatty acid-binding protein (L-FABP), netrin-1, cycle arrest biomarkers such as insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), endogenous ouabain (EO), selenium-binding protein 1 (SBP1) and BPIFA2 salivary protein (13). The majority of these biochemical markers are detected in urine. Compared to blood harvest for measurement of biomarkers urine harvest is noninvasive, accompanied by a reduced number of interfering proteins with an increased specificity for renal injury. In contrast to serum measurements, they have the disadvantages of the lack of samples from anuric patients, and the changes in the biomarker concentrations depending on the hydration status and diuretic therapy. Serum biomarkers avoid some of the urinary biomarker disadvantages. Nevertheless, their concentration can be modified by secretion from nonrenal sources and by subclinical changes in renal excretion (13).

Despite recent advances in characterization of new AKI biochemical markers, a few uncertainties limit their widespread clinical use: the timing for the measurement of AKI biochemical markers is not yet fully established; the significance of their increase can be mitigated by other clinical conditions such as an inflammatory status; the kinetics of their rise in different subset of patients including different ages groups is not sufficiently investigated; their expression profile may be different between various clinical settings such as CSA-AKI and sepsis-associated AKI. At present time, these limitations do not allow to justify the cost of these analyses in routine practice (14).

Beside biochemical markers of AKI, renal resistive index (RRI) is the most frequently measured biomechanical marker for detection of AKI at its early stage. The noninvasive assessment of RRI is performed by transparietal echography (TPE) or transesophageal echocardiography (TEE) during cardiac surgery by analyzing the intrarenal arterial Doppler waveform. It is derived from Doppler flow velocities as (maximal systolic velocity–minimum diastolic velocity)/maximal systolic velocity. Its value in general population

averages 0.6 and increases with age, female sex and body weight or body mass index but has an inverse relationship with body height (15). Several other factors affect the RRI value: (I) systemic hemodynamics directly influence RRI which increases with increasing pulse pressure and systolic or decreasing diastolic blood pressure as well as with reduced heart rate (15). In parallel to the latter condition, the use of beta-blockers induces a rise in RRI (15). In addition to blood pressure characteristics, total circulating blood volume and hence fluid management and cardiac output have been reported to inversely act on RRI (16); (II) Diabetes mellitus and atherosclerosis negatively impact the elasticity of the large as well as small vessel walls and thus are associated with increased RRI values in affected patients as compared to normal subjects (17,18).

Another biomechanical marker of AKI is represented by measurement of renal real-time regional oximetry by near-infrared spectroscopy. This technique has been reported in newborns undergoing cardiac surgery for congenital heart disease. The sensors were placed on the back of the babies at the level of T10–T12 left and right of the spine (19). However, because of the importance of the skin-kidney distance in infants and adults this technique has been so far used only in neonates younger than 12 months weighing less than 10 kg (19). In future, technological advances may make this method available in adults.

Given the noninvasiveness, relatively low cost and availability of RRI measurements compared to biochemical biomarkers determinations in the setting of cardiac surgery, several investigators have studied the value of RRI in predicting CSA-AKI (20–23). In a prospective observational study, Bossard and co-workers found in multivariate analysis a significant correlation between increased postoperative RRI upon arrival in the intensive care unit and the occurrence of postoperative AKI according to the RIFLE definition (20). They concluded that on the receiver operating characteristic (ROC) curve a value of RRI >0.74 allowed with a good sensitivity and specificity to predict CSA-AKI. The conclusion of this study should be considered with caution. The selection criteria included a series of known risk factors for development of AKI. Besides, pre-operative RRI was measured only in a small number of patients. Thus, pre-existing increased RRI could not be excluded. Interestingly, the incidence of AKI was similar between the studied group with risk factors for development of AKI and the entire patient population undergoing cardiac surgery during the same period (20). This raises the question of pertinence of

their selection criteria of risk factors for development of AKI. In another study, Guinot *et al.* reported a value of RRI >0.73 on the ROC curve to be predictive of CSA-AKI (21). The weaknesses of this study lie on the small number of investigated patients and the definition of AKI which was based on the sole increase of SCr levels. In a more recent study, Regolisti and collaborators observed a limited ability of intrarenal RRI measured by either TPE or TEE to predict CSA-AKI (22). On the ROC curve for RRI by either technique the AUC was 0.7–0.71. Moreover, combining RRI with serum NGAL at end-surgery did not provide a clear-cut advantage in predicting AKI (22). Comparable drawbacks of this study to the previous ones, i.e. small number of patients and the definition of AKI based on the sole increase of SCr levels, limit the relevancy of the conclusions. Using AKIN criteria for definition of AKI in a prospective observational study of patients undergoing cardiac surgery, Hertzberg *et al.* reported a weak predictive value for developing AKI according to an increased RRI >0.7 with a sensitivity of 0.78 and a specificity of 0.46 (23). Again, the small number of patients of this study renders its conclusion of limited applicability.

In a recent paper, Andrew and coworkers retrospectively studied the impact of aortic valve pathology on the preoperative RRI in an adult patient population undergoing cardiac surgery (24). An interesting finding of this study was that pre-operative aortic valve insufficiency per se was not associated with a higher incidence of AKI following corrective surgery. Moreover, they found that patients with aortic insufficiency and combined insufficiency/stenosis had higher median preoperative RRI values compared with patients without aortic valve pathology. Based on their findings, they cautioned about the potentially confounding effects of aortic insufficiency on renal flow patterns, independent of renal injury. Consequently, they recommended that pre-existing moderate to severe aortic valve insufficiency should be taken into account when using pre-operative RRI to predict post-operative AKI (24). The finding of Andrew and coworkers confirm earlier concerns that RRI might not accurately reflect renal resistance and renal blood flow in the presence of aortic valvular insufficiency (25). In this case, the renal artery diastolic velocity will be nearly 0. Thus, the RRI [(maximal systolic velocity–minimum diastolic velocity)/maximal systolic velocity] will be approximately 1, suggesting that renal blood flow has a very high resistance, leading possibly to an erroneous conclusion of possible renal dysfunction (25). Thus, in the presence of significant aortic insufficiency,

RRI might not accurately reflect renal flow resistance, resulting in an inaccurate impression of reduced renal blood flow from increased renal vascular resistance (25). The weaknesses of the Andrew's study lie on its retrospective character with small numbers. In contrast to the existing evidence (15), Andrew and coworkers did not find any correlation between age and gender and RRI (24). Another limitation to their study is the lack of information on pre-operative medication of the patients, particularly on diuretics and beta-blockers.

In summary, severe CSA-AKI is associated with increased perioperative mortality, prolonged length of stay in the ICU and in hospital, and increased cost of care following cardiac surgery. The risk of death and hospital readmissions associated with CSA-AKI remains high even 5 to 10 years after cardiac surgery regardless of other risk factors, even for those patients with complete renal recovery. Predictive risk models combining biochemical markers of AKI and RRI may allow early detection of AKI and thus prompt adaptation of therapeutic strategies to limit AKI and to improve prognosis. However, well-designed prospective randomized trials with adequate statistical power are still needed to address the value of each biomarker of AKI to be included in such a predictive model.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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